Intrinsic and network properties of interneuron diversity in the hippocampus

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Neuronal diversity in the cortex is the largest amongst GABAergic neurons. In the hippocampus, GABAergic cells have been sorted in several groups based on their morphology, firing patterns, connectivity, molecular profiling, and RNA content. It is thought that these specialized GABAergic groups aid specific circuit computations. Identification and manipulation of these distinct neuron types is a prerequisite to deciphering not only their role in circuit dynamics and behavior but also the computational mechanisms of the cortical networks they are embedded in.

To catalog the interneuron diversity in the hippocampal area CA1, we first grouped the virtual totality of GABAergic neurons into four major families, based on novel and standard genetic markers. Parvalbumin (PVALB)-expressing neurons, Somatostatin (SST)-expressing neurons, Vasoactive intestinal polypeptide (VIP) and Inhibitor of DNA binding 2 (ID2)-expression GABAergic cells comprised around 97% of CA1 GABAergic diversity. We then generated double and triple transgenic mice lines expressing channelrhodopsin (ChR) under the control of our four target genes (PVALB::Ai32, SST::Ai32, VIP::Ai80, and ID2/Dlx::Ai80). When necessary, we restricted the expression to only GABAergic cells by the intersection with distaless homeobox (Dlx) 5/6 to avoid expression in non-GABAergic cells. Using chronically implanted silicon probes coupled with optic fibers, we recorded and optogenetically identified large numbers of interneurons from these main four families in freely behaving mice (n = 3, 2, 3 and 4 mice for PVALB, SST, VIP and ID2/Dlx, respectively, >30 opto-tagged units per group). The four interneuron families show distinct intrinsic features and exhibited specific activity dynamics during NREM and REM sleep, theta oscillations, sharp-wave ripples, reward consumption and spatial exploration. Further subclasses within these four main families were identified by triple transgenic intersections (including ID2/Nkx2.1::Ai80, VIP/CCK::Ai80 and VIP/CR::Ai80), and validated with in vitro recordings and morphological reconstructions. Finally, we built an automatic classification tool based on the observed levels of complexity (waveform and auto-correlogram features, soma location, network interactions and brain state dynamics) which enable ground-truth-based classification of interneurons from hippocampal extracellular recordings. These experiments provided a high precision physiological characterization of interneuron types, a prerequisite for understanding their collective organization for supporting circuit computation.